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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/566,724	02/02/2006	Tomohiro Kono	16910214PUS1	9720

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EXAMINER	
BERTOGLIO, VALARIE E	

ART UNIT	PAPER NUMBER
1632	

NOTIFICATION DATE	DELIVERY MODE
03/18/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/566,724	KONO ET AL.	
	Examiner	Art Unit	
	Valarie Bertoglio	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 February 2006* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/06;05/06;02/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The instant application is a 371 of PCT/JP04/11491, filed 08/04/2004, which claims priority to Japanese Patent Application 2003-286543, filed 08/05/2003.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119 as follows:

Should applicant desire to obtain the benefit of foreign priority under 35 U.S.C. 119(a)-(d) prior to declaration of an interference, a certified English translation of the foreign application must be submitted in reply to this action. 37 CFR 41.154(b) and 41.202(e).

Failure to provide a certified translation may result in no benefit being accorded for the non-English application.

Specification

Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of **50 to 150 words**. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

Claim Objections

Claim 5 is objected to because of the following informalities: Claim 5 appears to fail to differ in scope from claim 1 or 4. Claim 5 requires the gene deleted ovum be derived from a gene

deleted mammal. However, it appears there is no other means of obtaining such an ovum. Thus, claim 1 is no broader than claim 5. Appropriate correction is required.

Claim Rejections - 35 USC § 112-1st paragraph

Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of constructing a parthenogenetic mouse zygote, (mouse embryo or mouse), the zygote having a haploid genome set derived from nongrowing (ng) ovum and a haploid genome set from fully-grown (fg) ovum, which comprises the steps of

(1) introducing a mouse primitive ovarian follicle egg (ng ovum) whose haploid genome lacks the H19 gene into an enucleated mouse oocyte at germinal vesicle stage and developing the resulting oocyte to MII phase by in vitro maturation and culture to prepare a first nucleus-implanted egg, and

(2) extracting the MII phase nucleus from said first nucleus-implanted egg and introducing it into a second MII phase egg (fg ovum) to prepare a second nucleus-implanted egg,

does not reasonably provide enablement for the claimed method in any species other than mouse or for use of any ng oocyte nucleus other than those lacking the H19 gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

. Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the

breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

Parthenogenetic mammalian embryos carrying haploid genomes from non-growing (ng) and fully grown (fg) oocytes can not develop past 13.5d gestation. Kono (2002, IDS) taught that the block to development is an effect of biallelic expression of H19 that prevents expression of IGF2 in the embryo that results when H19 enhancers are preferentially used, out-competing the same elements needed for expression of IGF2 (see page 295, col. 1, paragraph 1). The instant invention overcomes this block to development by use of an 'ng' nucleus, which demonstrates 'male-like' imprinting and is deficient for the H19 gene and an 'fg' nucleus that is wildtype.

The claims broadly encompass use of the claimed method in any mammalian species, use of an $H19^{+}$ ng nucleus and use of a nucleus whose genome lacks genes other than H19. The specification teaches use of an ng nucleus from a mouse whose genome lacks the H19 gene.

As discussed by Kono (2004, IDS), use of a wildtype ng nucleus results in developmental arrest at 13.5d as a result of activity at both copies of the H19 gene that occurs from a lack of proper imprinting. Deletion of the H19 from the ng genome results in only one active H19 gene in the embryo, which allows for normal expression of IGF2 (see paragraph bridging pages 860-861). As discussed by Kono, removal (or silencing) of one copy of H19 is necessary for appropriate expression of IGF-2. Otherwise, development will not proceed. H19 and IGF-2 share a regulatory element as the two genes are adjacent on the chromosome and H19 is preferentially expressed. The specification does not teach that deletion of any imprinted gene will have the same effect as the deletion of H19. It is clear that proper regulation of IGF2 is necessary for development and this is only obtained by turning off expression of H19 on one chromosome. There is no evidence of record that indicates that knockout of any gene other than H19 will lead to proper regulation of IGF2. Furthermore, it is necessary that H19 be deleted for the claimed method to produce a live offspring. No claim requires the deletion of H19. Claim 1 does not require a live offspring, however, the specification sets forth that the utility of the invention lies in making an adult

parthenogenetic mammal (see para bridging pages 15-16). Thus, the claimed methods fail to have an enabled *use* if the methods, as claimed, cannot result in a live mammal.

To the extent that the claimed method requires use of oocytes from a knockout animal lacking the H19 gene, the specification and art at the time of filing were only enabling for use of mice. Gene-targeting by homologous recombination could not be used to make an animal of any species other than mouse. At the time of filing and presently, in vivo gene-targeting required homologous recombination in cells in vitro. The only cells that can be cultured in vitro that are competent to populate the germline and thereby make an animal are mouse ES cells. ES cell use for the generation of genetically modified animals with germline transmission, such as knockin or knockout animals, has only been established in mice. Denning and Priddle state, "…pluripotent embryonic stem (ES) cells, which have been central to success in mice, are not available in any domestic species, despite considerable efforts to isolate them." (**Reproduction** 126:1, col 2, par 1, 2003). Since the art does not teach a means of making knockout or knockin mammals other than in mice, an artisan would look to the specification for specific guidance on how to make knockin or knockout mammals other than mice. However, the specification only provides specific guidance the mouse. Given the lack of guidance in the art and specification for producing knockin/knockout mammals, an artisan would not know how to use/make the instant invention with any other mammal than the mouse. Therefore the instant specification is not enabled for any other mammal or mammalian ES cell other than mouse and mouse ES cells.

With regard to the claim breadth directed to any non-human mammal, the specification fails to teach the production of any transgenic non-human mammal, other than mouse, whose genome comprises a disruption in the adiponectin gene. At the time of filing and presently, gene-targeting in vivo required homologous recombination in cells in vitro. The only cells that can be cultured in vitro that are competent to populate the germline and thereby make an animal are mouse ES cells. Thus, ES cell use for the generation of genetically modified animals with

germline transmission, such as knockin or knockout animals, has only been established in mice. Denning and Priddle state, "…pluripotent embryonic stem (ES) cells, which have been central to success in mice, are not available in any domestic species, despite considerable efforts to isolate them." (**Reproduction** 126:1-11, 2003, specifically page 1, col 2, par 1, 2003). Similarly, Smith **(Journal of Biotechnology,** 99:1-22, 2002**)** teaches that mouse was the only species for which technology was available to successfully create gene targeted/knockout animals:

> ES cell technology has enabled a large range of transgenic approaches in the mouse. Types of gene modifications presently available in the mouse include targeted elimination of endogenous gene expression (gene 'knockout'), targeted gene repair/replacement, conditional gene targeting and 'gene trap' reporter systems.

The use of ES cells is limited due to the fact that, to date, the mouse is the only animal from which ES cell lines have been unequivocally established. It would be surprising if this limitation represents a fundamental biological barrier. However, further empirical work is needed before true ES cell lines become available for other species. It is possible that the inbred strains of mice used to generate ES cells may carry mutations that are essential for the generation of ES cells. If such mutations represent a precondition for ES cell derivation, then it may take a considerable amount of time to establish nonmurine ES cell lines. Such progress is expected to have a positive impact on nonmurine ES cell establishment. When nonmurine ES cells become available, the established mouse technologies will provide the basis for in vitro genetic modification of all species (page 3: col. 1, paragr. 3 to col. 2, line 11; emphasis added).

Claim Rejections - 35 USC § 112-2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is unclear. The metes and bounds of the terminology "gene modification posteriori" in claim 1 are unclear. The specification fails to set forth what is encompassed by the terminology and it does not appear to be a term used routinely with a well-accepted definition in the art. Claims 2-7 depend from claim 1.

Claim 1 is further unclear because of the use of the term "them" at line 7.

The terminology "MII phase chromosome" at step (2) is also unclear as the specification teaches extracting the entire nucleus and not just a chromosome. It is not know if it is intended that one chromosome, multiple chromosomes, or all chromosomes be extracted. The terminology also lacks clear antecedent basis as it can not be determined which MII phase chromosome is extracted.

Claim 6 recites the limitation "activating the second nucleus-implanted gene" in lines 2-3. There is insufficient antecedent basis for this limitation in the claim. Claim 7 depends from claim 6.

Claims 6 and 7 are unclear because it is not known what is intended by the last term in the claim, "same".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-7 are rejected under 35 U.S.C. 102(a) as being anticipated by Kono (2004, IDS).

Kono taught generation of parthenogenetic mice by introducing an ng ovum from a neonatal (claim 2) mouse whose genome comprises a 13kb deletion of the h19 gene (claim 4). After in vitro maturation, the h19 deleted nucleus (MII phase chromosome) was transplanted into an intact enucleated GV oocyte (claim 3) which was then parthenogenetically activated (see page 863, col. 1, paragraph 3-4). The parthenogenetically activated zygotes were then grown through blastocyst stage and transplanted into the uterus of a female mouse where they progressed through to birth (claims 6 and 7).

Applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

Thus, Kono (2004) anticipates claim 1-7.

Claims 1-7 are rejected under 35 U.S.C. 102(b) as being anticipated by Kono (2002, IDS).

Kono taught generation of parthenogenetic mice by introducing an ng ovum from a neonatal (claim 2) mouse whose genome comprises a 3kb deletion of the H19 gene (claim 4). After in vitro maturation, the H19 deleted nucleus (claimed as'MII phase chromosome') was transplanted into an intact enucleated GV oocyte (claim 3) which was then parthenogenetically activated (see page 295, col. 1, paragraph 3-4; col. 2, paragraph 1). The parthenogenetically

activated zygotes were then grown through blastocyst stage and transplanted into the uterus of female mice where they progressed through to birth (claims 6 and 7).

Thus, Kono (2004) anticipates claim 1-7.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is (571) 272-0725. The examiner can normally be reached on Mon-Thurs 5:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Valarie Bertoglio, Ph.D./
Primary Examiner
Art Unit 1632